REMARKS/ARGUMENTS

Claims 1-35 are pending in the subject application. Of these, claims 5, 6, 9, 13, 14, 21, 22, 24, and 25 have been withdrawn from consideration. Thus claims 1-4, 7-8, 10-12, 15-20, 23, and 26-35 are currently under consideration.

Claim 23 has been amended to correct a minor punctuation error. Claims 1 and 26 has been amended, and new claims 36 and 37 have been added, to better define the invention by explicitly describing the sources for the protein domains in the claims. Support for the new claims and the claim amendments can be found in the specification as filed, at for example paragraphs 0029 and 0038 in the specification as filed.

I. Rejections Under 35 USC 112, second paragraph:

In the Office Action mailed March 27, 2007 The Examiner rejected Claims 1-4, 7-8, 10-12, 15-20, 23, and 26-35 under U.S.C. 112, second paragraph.. The Examiner stated that because "Ret receptor kinase" and other receptors disclosed in the instant application are identified by name, and not by structure, that the metes and bounds of the terms used are allegedly not clear.

In response, applicants respectfully disagree. The Ret receptor kinase is a well-known and well characterized receptor tyrosine kinase, with which one of ordinary skill in the art (i.e. oncology; drug discovery) would be familiar. There is only one gene coding for Ret in the animal species that have been studied. In the instant application multiple references are given when referring to Ret, all of which clearly describe what is meant by Ret receptor kinase, including for example in paragraphs 0010 (in "Background") and 0027 (in "Detailed Description"), in the application as filed. For example, three of these are attached as Exhibits A (Arlt, D.H. et. al., 2000, Oncogene, 19:3445-3448), B (Bongarzone, I. et. al., 1999, Oncogene 18:4833-4838), and C (Rizzo, C. et. al., 1996, J. Biol. Chem. 46:29497-29501). All three of these unambiguously identify what is meant by "Ret receptor kinase" by both the work described therein and the body of work that they reference (e.g. see Introduction sections). Thus it is not necessary to define what is meant by the term

"Ret receptor kinase" in structural terms as there is no ambiguity likely to be created by the use of this term.

In support of the position that "Ret receptor kinase" is well known in the art, applicants also submit information from several sources that were searched for the term "Ret". In Exhibit D, the first few hits from a search of the NCBI Gene Database for Ret are listed. They are the Ret proto-oncogenes, coding for the Ret receptor kinase, from the fly Drosophila, human, rat, dog, mouse, chicken, and chimpanzee. On examination one would find that they are each the same gene in the respective species and are thus all very closely related. No other Ret receptor kinase genes were identified that could cause confusion as to the meaning of the term "Ret receptor kinase". The entry for human Ret was further expanded (see Exhibit E), which provided further extensive information and references describing Ret receptor kinase. All of this work describes essentially the same "Ret receptor kinase" (albeit with variants, but encoded by the same Ret gene), and is absolutely unambiguous as to the meaning of the term "Ret receptor kinase". The instant specification (e.g. paragraph 0033) also indicates that the complete sequences of Ret receptor kinase proteins and their encoding DNAs from multiple species are available in public databases such as Genbank.

Exhibit F shows several entries from Cancer Principles and Practice of Oncology 6th Edition, 2001), edited by Vincent T. DeVita et al., a standard and well-respected text in oncology, authored by many of the leaders in this field (see pages vii-xxii). On the Index page (I-136) it can be seen that there are multiple entries for Ret. The first of these, on page 18, from Chapter 2, on "Essentials of Molecular Biology: Genomics and Cancer", describes cancer genes, and Ret, in addition to ras and the retinoblastoma gene, are the first three genes mentioned. Chapter 38 (p. 1730-1732; attached) goes on to describe the Ret gene, and mutations therein, in considerable more detail. It is clear from this description that this is the same Ret kinase to which the instant application refers.

Furthermore, even when searching for Ret on the internet using the Google™ search engine, the second hit is a Wikipedia entry for Ret proto-oncogene coding for a receptor tyrosine kinase, which describes in detail (see Exhibit G) the properties of Ret kinase, including the three characteristic domains (i.e.

extracellular, transmembrane and cytoplasmic kinase domains) as described in the instant application. Thus, even a common source of information outside of the specialized texts and databases frequented by oncologists and other medical researchers has an entry for "Ret receptor kinase". Yet again, inspection of the information presented reveals the same Ret gene and encoded kinase as referred to in any of the documents above, including the instant application. No other Ret kinase genes are described.

In the context in which the term is being used in the application, Ret receptor kinase is used as a descriptor for any of the Ret receptor kinase proteins coded for by the Ret gene, irrespective of the species. The essential requirement of the Ret extracellular domain of the instant invention is that it possesses an activating modification(s) that confer the ability to activate a heterologous kinase domain in a ligand-independent manner, as described in the instant specification and claims. Thus "Ret receptor kinase" as described in the claims is not a single structure, but is a closely related family of structures encoded by Ret genes from different species. This is made clear by, for example, paragraph 38 which states: "In the practice of this invention, the hybrid receptor components can originate from any species whose genome encodes the appropriate receptor protein-tyrosine kinase component" and "The species of origin for the Ret domain is preferably selected from human, mouse, rat, or primate, but can be from any other species possessing a Ret receptor." Suitable Ret extracellular domains that possess activating modification(s) that confer the ability to activate the heterologous kinase domain in a ligand-independent manner, or ways to produce such in Ret proteins from human or other animal species, are described in detail in the application as filed at paragraphs 27-30.

In order to further clarify the meaning of the claims as described in the preceding paragraph applicants have also amended claims 1 and 26 to explicitly indicate that the extracellular domain of Ret receptor kinase can originate from any species whose genome encodes a Ret receptor kinase.

Applicants would like to also respectfully note that although the Examiner has indicated that the term "Ret receptor kinase" is allegedly ambiguous, he has not identified any other "Ret" receptor kinases that could be a cause for ambiguity in

understanding what is meant by the term "Ret receptor kinase". Applicants are only aware of one Ret gene in any given species that has been studied to date, and in view of the arguments and amendments above believe that the term "Ret receptor kinase" is clear in the context used.

With respect to other receptor domains from receptor protein-tyrosine kinases that are recited by name (e.g. in paragraph 0033), applicants note that all of these receptor protein-tyrosine kinases, like Ret, are well known and in the public domain, and thus there is no ambiguity as to what is meant by the terms used. As indicated in paragraph 0033, for example, "The complete sequences of these proteins and their encoding DNAs from multiple species are available in public databases, e.g. Genbank." Also, as with Ret, the instant specification clearly indicates, at for example paragraph 38, that "In the practice of this invention, the hybrid receptor components can originate from any species whose genome encodes the appropriate receptor protein-tyrosine kinase component." However, in order to further clarify the meaning of the claims, applicants have also amended claims 1 and 26 to explicitly indicate that the kinase domain of the heterologous receptor protein-tyrosine kinase can be from any receptor protein-tyrosine kinase of any species.

Accordingly, in view of the above arguments and amendments, applicants respectfully submit that all rejections under 35 USC 112 have been overcome and request their withdrawal.

II. Rejections Under 35 USC 102

In the Office Action mailed March 27, 2007 The Examiner rejected Claims 1-4, 7-8, 10-12, 15-20, 23, and 26-35 under U.S.C. 102(b), as being anticipated by Rizzo et al. (1996) J. Biol. Chem. 271(46):29497-29501. The Examiner stated that Rizzo et al. discloses a hybrid receptor which is an EGFR/RET chimera (on pages 29498-29499), and that the "claim limitations do not exclude the receptors of Rizzo et al. because the claims recite receptors by name only."

In response, applicants respectfully point out that the chimeric receptors disclosed in Rizzo et al. are composed of an extracellular domain of EGFR fused to a

catalytic kinase domain of Ret, wherein either a wild type Ret kinase domain or a mutant Ret kinase domain (i.e.MEN2B Ret) with a single point mutation that confers constitutive activity is used. In either case, the ligand EGF was used to activate the activity of the Ret kinase domain, and the effects of Ret kinase on cells could thus be investigated. In contrast, applicants hybrid receptor as described in the claims of the instant invention comprises a Ret extracellular domain fused to the kinase domain of a heterologous receptor kinase, wherein the Ret extracellular domain comprises a modification that confers constitutive, ligand-independent activity on the hybrid receptor kinase. In the instant invention, in contrast to Rizzo et al., the Ret extracellular domain of the hybrid receptor confers ligand independent activity, and for example allows one to investigate the cellular effects of the heterologous kinase domain. In Rizzo et al. EGFR is used as the extracellular domain in order to confer EGF-activation on the Ret kinase domain of the hybrid receptor. Rizzo et al. do not disclose any hybrid receptor that uses a Ret extracellular domain comprising a modification that confers constitutive, ligand-independent activity on the hybrid receptor kinase, and thus cannot anticipate the instant invention.

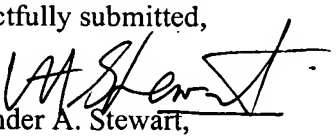
Accordingly, in view of the above arguments, applicants respectfully submit that all rejections under 35 USC 102 have been overcome and request their withdrawal.

III. Conclusion

In view of the arguments and amendments set forth above, ppplicants respectfully request that the Examiner reconsider and withdraw the various grounds of rejection, and that a timely Notice of Allowance be issued in this case.

Agent for Applicants can be reached at the telephone number and address below.

Respectfully submitted,



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